Am. J. Hum. Genet. 54:403–413, 1994

1993 American Society of Human Genetics Presidential Address: Can We Meet the Challenge?

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I must begin today's address by expressing my own sense of outrage and that of all members of the Society regarding the wanton attack on our colleague, Charles Epstein. As Editor for the last 7 years, Charlie has been a major force in seeing that the forefront of genetic research is presented in the Society's *Journal*. The *Journal* under Charlie's stewardship has devoted an increasing number of pages to molecular genetics, while at the same time encouraging the publication of high-quality articles on clinical genetics, population and statistical genetics, as well as on the ethical issues that are becoming increasingly vexing and difficult to resolve. The diversity of *Journal* articles mirrors the diversity of our Society. The unconscionable attack on Charlie is, in one sense, an attack on all of us, even though we do not know the motive for selecting him rather than a number of other scientists or geneticists.

The attack on David Gelernter is equally mystifying and reprehensible. As I just said, we do not know whether the attack was motivated by Charlie's association with genetics and whether David was mistaken for his brother Joel, who is also a geneticist. Despite these attacks, we must maintain our resolve to continue our research efforts, which have flourished in the last decade as never before. As members of the Society know, we, along with other involved groups, have been asked by the FBI to pledge our money toward a reward of $1,000,000.00 that would be given to an individual who supplied the critical information leading to the arrest and conviction of the perpetrator of these crimes. To date the Society has pledges of over $15,000.00; other organizations have pledges totaling over $350,000.00. To those of you who have responded, I offer my sincere thanks. To those of you who have not pledged and would like to do so, forms are available.

I chose the title of my address in part to be provocative and to pique your curiosity but also because I believe that we as a Society have recently passed some major "watersheds." Thus, it is an appropriate time to look to the future, as we assess the impact of recent organizational decisions upon the responsibilities, as well as on the goals of and opportunities presented to our Society. Some of you have been involved in the strategic planning process initiated by Maimon Cohen; it will be his responsibility as President next year to review the various proposals for future changes and to present the suggestions with some sense of priority for implementing the various components of the strategic plan. Few members of the Society are as well qualified as Maimon to accomplish this task.

On the basis of the most objective current criteria, the Society is doing very well. We have 3,500 registrants at this meeting; considering the circumstances, this compares favorably with almost 3,800 scientific registrants at last year's meeting in San Francisco. Fortunately, the very restrictive abortion laws that caused concern about a New Orleans meeting were declared unconstitutional. We can enjoy the charm of this city without the sense of guilt that might well have oppressed this meeting.

We are numerically, intellectually, and scientifically stronger than we have ever been. Moreover, we are in a remarkable position to exploit this strength. As a member of the Society since 1963, I can recall some of the issues that were of concern at that time. I remember a sense of fragmentation of human genetics. There were some of us who were cytogeneticists, others who were clinical geneticists or dysmorphologists, or population geneticists, or biochemical geneticists. It seemed as though each group was going its own way, with little

Received November 22, 1993. This address was delivered October 7, 1993, in New Orleans.

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0002-9297/94/5403-0002$02.00

Table 1

Recurring Structural Rearrangements in Malignant Myeloid Diseases

Disease	Chromosome Abnormality	Involved Genes
Chronic myeloid leukemia	t(9;22)(q34;q11)	*ABL-BCR*
Blast phase	t(9;22) with +8, +Ph +19, or i(17q)	*ABL-BCR*
Acute myeloid leukemia:		
AML-M2	t(8;21)(q22;q22)	*ETO-AML1*
APL-M3, M3V	t(15;17)(q22;q12)	*PML-RARA*
AMMoL-M4Eo	inv(16)(p13q22) or t(16;16)(p13;q22)	*MYH11-CBFB*
AMMoL-M4/AMoL-M5	t(9;11)(p22;q23)	*AF9-MLL*
	t(10;11)(p11-p15;q23)	*?-MLL*
	t(11;17)(q23;q25)	*MLL-?*
	t(11;19)(q23;p13)	*MLL-ENL*
	other t(11q23)	*MLL*
	del(11)(q23)	
AML	t(6;9)(p23;q34)	*DEK-CAN*
	t(3;3)(q21;q26) or inv(3)(q21q26)	*?-EVI1*
	+21	
	−7 or del(7q)	
	−5 or del(5q)	
	del(20q)	
	t(12p) or del(12p)	
	−Y	
Therapy-related AML	−7 or del(7q) and/or −5 or del(5q)	*IRF1?*
	t(11q23)	*MLL1*
	t(3;21)(q26;q22)	*EAP/MDS1/EVI1-AML1*
	der(1)t(1;7)(q10;p10)	

sense of scientific commonality. Granted that we all studied human material and that we were trying to use our skills and our research to further the understanding of the genetic basis of human disease. There was a sense, nonetheless, that each specialty would be almost as strong as an independent entity as it was as an element remaining within the Society. This flirting with separation subsided in the 1970s as the interrelatedness and the complementarity of all of these specialties became so apparent.

In the 1970s other problems arose, one of the most critical being quality control. Anyone could set up a cytogenetics laboratory and analyze amniotic fluid samples or other samples for chromosome abnormalities. Yet errors, either finding abnormalities where none existed or failing to detect an abnormality, had potentially serious consequences for the family. Similar errors in diagnostic biochemical studies or inadequate clinical evaluation or incompetent counseling of families—all were sources of major concern for members of the Society. As a consequence, after long assessment of the situation and consultation with other organizations, the American Board of Medical Genetics was established. This organization assumed the responsibility for quality control by developing and administering examinations to evaluate the competence of individuals and by certifying training programs. The first examination was given in 1982. The Board also tried to make genetics a more recognized component of medicine through interactions with other organizations, especially in pathology and laboratory medicine. However, it became apparent by the end of the 1980s that genetics was still a stepchild in medicine, often ignored or denigrated by recognized medical specialties. Again as the result of an assessment of the options, it was decided to apply for membership in the American Board of Medical Specialties. When this application was approved, it became clear that the price for admission was much higher than was initially anticipated. The AMA would allow our Board to certify Ph.D.s, but not master's-level geneticists and genetic counselors. Charlie Epstein described the history of these negotiations very candidly at an informational meeting last year. The genetic counselors felt, not without some justification, that they were abandoned. To resolve this crisis for the Society, the Society has agreed to provide substantial financial assistance to the newly formed American Board of Genetic Counseling for the next 10 years, so that it could give

Table 2

Cytogenetic-Immunophenotypic Correlations in Malignant B-Lymphoid Diseases

Phenotype	Chromosome Abnormality	Involved Genes
Acute lymphoblastic leukemia:		
Pre-B	t(1;19)(q23;p13)	*PBX1-TCF3(E2A)*
B(SIg+)	t(8;14)(q24;q32)	*MYC-IGH*
	t(2;8)(p12;q24)	*IGK-MYC*
	t(8;22)(q24;q11)	*MYC-IGL*
B or B-myeloid	t(9;22)(q34;q11)	*ABL-BCR*
	t(4;11)(q21;q23)	*AF4-MLL*
Other	50–60 chromosomes	
	t(5;14)(q31;q32)	*IL3-IGH*
	del(9p),t(9p)	
	del(12p),t(12p)	
Non-Hodgkin lymphoma:		
Burkitt type	See SIg+ ALL	*MYC-IGH-IGK-IGL*
Follicular	t(14;18)(q32;q21)	*IGH-BCL2*
Mantle cell	t(11;14)(q13;q32)	*CCND1-IGH*
Diffuse large cell	t(3;14)(q27;q32)	*BCL6-IGH*
	t(10;14)(q24;q32)	*LYT10-IGH*
Chronic lymphocytic leukemia	t(14;14)(q13;q32)	*CCND1-IGH*
	t(14;19)(q32;q13)	*IGH-BCL3*
	t(2;14)(p13;q32)	*IGH*
	t(14q) and/or +12	
Multiple myeloma	t(11;14)(q13;q32)	*CCND1-IGH*

certifying examinations and could assume other appropriate responsibilities with some sense of stability. Financial support was also provided by the Board and the College.

Thus for the first time in quite a while, the Society is free to turn its attention to **human genetics.** This doesn't mean that it can abandon its responsibility for assisting in the rapid transfer of scientific discoveries into clinical practice and for vigilance regarding the complex ethical issues that surround the application of genetic discoveries in clinical situations. I think it is fair to say, however, that we can function now more as an advisor or a collaborator than as a direct actor in some of these matters.

The number of organizations that have some involvement in genetics may surprise you. In fact, there is now an organization, called "COMEGO" (Council of Medical Genetics Organizations), that has the following organizations as members:

1. Alliance of Genetic Support Groups
2. American Board of Genetic Counseling
3. American Board of Medical Genetics
4. American College of Medical Genetics
5. American Society of Human Genetics
6. Association of Cytogenetic Technologists
7. Association of Professors of Medical and Human Genetics
8. Canadian Association of Genetic Counselors
9. Canadian College of Medical Genetics
10. Council of Regional Networks
11. International Society of Nurses in Genetics
12. National Society of Genetic Counselors
13. Royal College of Physicians and Surgeons
14. Society of Craniofacial Genetics

It meets every 6 months to discuss issues of mutual interest and to develop unified positions on some of these issues. Fortunately COMEGO met in late March, when the Task Force on Health Care was also meeting in Washington. Libby Short, the chairman of the Public Policy Committee, was a member of the task force, and she expressed her concern that the very special needs of patients with various genetic diseases might not be receiving adequate attention from the task force. The representatives of the organizations comprising COMEGO drafted a fact sheet on the spot to be sent to the task force regarding the need for access to adequate genetic health care services for families with genetic disorders. As President of the Society, in collaboration

Table 3

Cytogenetic-Immunophenotypic Correlations in Malignant T-Lymphoid Diseases

Phenotype	Chromosome Abnormality	Involved Genes
Acute lymphoblastic leukemia	t(1;14)(p32;q11)	*TAL1-TCRD*
	t(11;14)(p15q11)	*RBTN1-TCRA*
	t(11;14)(p13;q11)	*RBTN2-TCRA*
	t(8;14)(q24;q11)	*MYC-TCRA*
	inv(14)(q11q32)	*TCRA-IGH*
	t(10;14)(q24;q11)	*HOX11-TCRA*
	t(1;14)(p34;q11)	*LCK-TCRD*
	t(7;9)(q35;q32)	*TCRB-TAL2*
	t(7;9)(q35;q34)	*TCRB-TAN1*
	t(7;7)(p15;q11)	*TCRG-?*
	t(14;14)(q11;q32)	*TCRA-IGH*
	t(7;14)(q35;q11)	*TCRB-TCRD*
	t(7;14)(p15;q11)	
Non-Hodgkin lymphoma:		
T	see T-cell ALL	
	t(4;16)(q26;p13.1)	*IL2-BCM*
T or B(Ki-1+)	t(2;5)(p23;q35)	*NMP-ALK*
Chronic lymphocytic leukemia	t(8;14)(q24;q11)	*MYC-TCRA*
	inv(14)(q11q32)	*TCRA/D-IGH*
Adult T-cell leukemia	t(14;14)(q11;q32)	*TCRA-IGH*
	inv(14)(q11q32) +3	*TCRA/D-IGH*

with other COMEGO presidents, and following up on Nancy Wexler's conversation with Hillary Clinton, we have sent a letter to Mrs. Clinton reiterating the necessity for universal health care to protect those with genetic risk factors from being uninsurable. As I said earlier, with what is, in a sense, a shedding of some of these responsibilities, the Society can and should focus on the issues of research into the genetic basis of disease and into the most effective means of bringing the discoveries made at the laboratory bench to the clinic. The strength of our Society is its diversity, the broad range of interests and of skills represented by our members. An important aspect of our diversity is our international nature. Twenty percent of our members are from other countries. We hope in the future to establish closer ties with genetics societies outside of the United States. The Society must recognize and foster this diversity, both in the programs prepared for this annual meeting and in its *Journal.*

We should applaud the efforts of Bronya Keats and her Program Committee for introducing a number of new events here in New Orleans. First, on Monday, 25 high school teachers brought 50 students for an all-day program—part lecture, part hands-on demonstration —supported by four of our exhibitors. The education sessions on Wednesday morning were new, and some of these were standing room only. Clearly they filled a need. The public meeting tonight at 6:30 on the "Genetic Health of our Children" is also new. I urge you all to attend. The session on Saturday, "Late Breaking Research Results" is another first. Many of these innovations will become a regular feature of our annual meetings.

The research efforts of Society members are proceeding on many fronts. I want to concentrate today on the subject with which I am most familiar, namely, cancer. In my opinion, cancer is *the* most common genetic disease, and the major application of many of the diagnostic tests that are being developed today will be in cancer (Rowley et al. 1993). The genetic component of cancer has two aspects; one involves the spontaneous changes in genes, and the other, an inherited predisposition to cancer. Most people probably do not have a predisposition, and the changes that occur affect normal genes that are mutated to defective genes which, in combination, lead to cancer. Here the challenge for scientists is to discover the various genes that are involved, to determine how the alterations lead to a malignant cell,

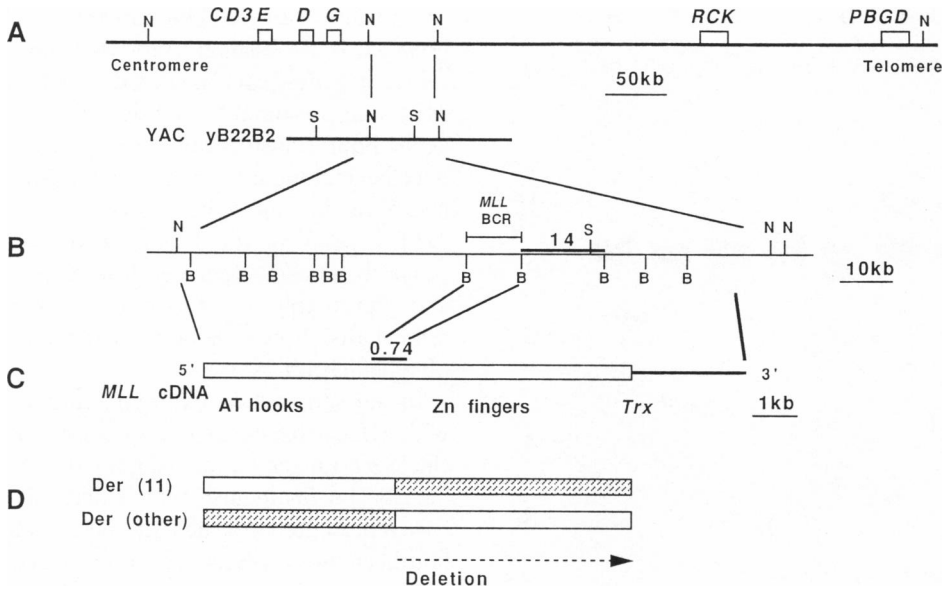

Figure 1 *A*, Partial map of 11q23, showing the location of nearby genes. *Below*, Partial restriction map of YAC, showing alignment to larger genomic map above and to the *MLL* gene in *B*. *B*, Partial map of *MLL*, showing the location of the 8.3-kb breakpoint cluster region (BCR) and the clone 14 probe used in FISH studies. *C*, Diagram of the cDNA with the position of the 0.7-kb probe and the general location of important motifs. *D*, Representation of the two derivative chromosomes formed as a result of the translocation. The zinc fingers are translocated to the der(other) chromosome, and part or all of *MLL* telomeric to the breakpoint is deleted in about 25% of de novo acute leukemia patients. N = *Not*I; S = *Sfi*I; B = *Bam*HI; Zn fingers = zinc fingers; *trx* = *trithorax;* der(11) = derivative 11 chromosome; and der(other) = other derivative chromosome.

and how to detect these genetic changes accurately and at a reasonable cost.

In the Allan Award Lecture that I presented in 1991, I described my efforts and those of my colleagues to identify the genes that were involved in chromosome translocations in leukemia and lymphoma. Collectively, we have been remarkably successful, and I believe it is fair to say that the breakpoints of virtually all of the important translocations in hematologic conditions have been cloned (tables 1–3). Suitable DNA probes are now or soon will be available for the diagnosis of these rearrangements, using either fluorescence in situ hybridization (FISH) or Southern blot or the polymerase chain reaction (PCR). This is a major accomplishment—an accomplishment contributed to by scientists from around the world.

I would like to bring you up to date very briefly on our progress in analysis of the gene *MLL* (myeloid-lymphoid leukemia), involved in 11q23 translocations, which was identified in my laboratory in 1991. Abnormalities of 11q23, usually translocations, are of interest for a number of reasons. First, rearrangements involving chromosome band 11q23 are very common in acute leukemia, both lymphoblastic and myeloid (monoblastic), and are less common in lymphoma. Although several different genes have been cloned from translocation breakpoints in leukemias, the great majority of translocations involve the *MLL* gene. Thus rearrangements involve 11q23 and at least 30 other chromosomal bands and therefore (presumably) 30 other genes (Thirman et al. 1993*a;* Rowley, in press). Moreover these aberrations are seen with an incredibly high frequency in infants with leukemia under 1 year of age. In fact, translocations involving 11q23 are the single most common cytogenetic abnormality in infants with acute leukemia, regardless of phenotype (Raimondi 1993). Finally, cancer patients who previously received drugs that inhibit topoisomerase II often develop acute leukemia with translocations involving 11q23 (Pedersen-Bjergaard and Philip 1991; Ratain and Rowley 1992).

This has been an extraordinarily popular translocation breakpoint which has been cloned independently and almost simultaneously by half a dozen laboratories. Unfortunately, many laboratories have given the gene their own name (e.g., *ALL1, Htrx,* or *HRX*) (Cimino et al. 1991; Djabali et al. 1992; Tkachuk et al. 1992, respectively), which is creating endless confusion in the literature. The *MLL* gene (I am using the symbol ac-

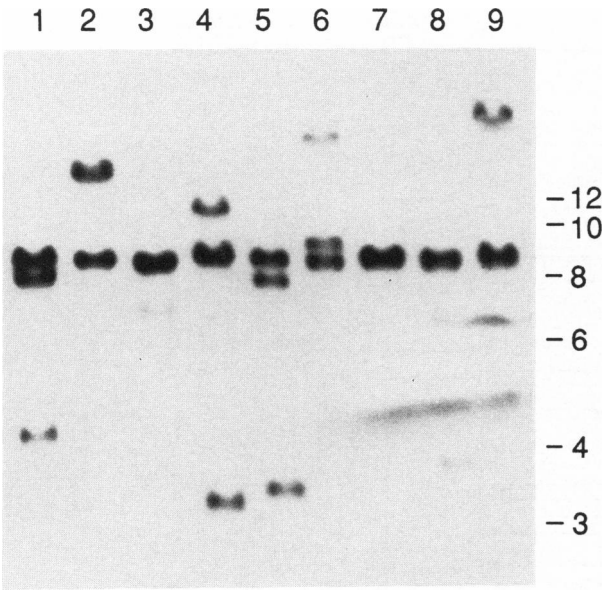

Figure 2 *Bam*HI-digested DNA from patients with a t(11;19) (lanes 1–6) or with a t(6;11) (lanes 8–9), probed with the 0.7-kb *Bam*HI cDNA. Lane 7 is the control. Lanes 1 and 4–6 have two rearranged bands, whereas lanes 2, 3, 8, and 9 have a single rearranged band, indicating a deletion of *MLL* telomeric to the breakpoint.

cepted by the Human Genome Nomenclature Committee) is a very large gene with RNA transcripts ranging in size from 15 kb to about 2 kb. The gene is transcribed from centromere to telomere. It is expressed in a wide variety of human tissues. The gene has some regions of homology to the *Drosophila trithorax* gene, especially in its central part that contains motifs coding for zinc fingers which could potentially bind DNA.

We isolated a 0.74-kb *Bam*HI fragment from a cDNA subclone of *MLL* (Thirman et al. 1993*a*). This fragment was composed of exons located at the centromeric and telomeric ends of an 8.3-kb genomic *Bam*HI fragment of the *MLL* gene on Southern blot analysis in 61 patients (58 with leukemia and 3 with lymphoma) by using the 0.74-kb cDNA fragment as a probe (fig. 1). The probe identified rearrangements in all 46 samples of DNA from patients with the common translocations involving 11q23. We also identified similar *MLL* gene rearrangements in DNA from 10 patients with several less common 11q23 translocations listed by Mitelman (1992), as well as from 5 other patients with 11q23 anomalies not reported in this catalog.

Thus we have detected 21 different translocations in our laboratory, and other laboratories have identified 8 other translocations (Thirman et al. 1993*a;* Rowley, in press). It is astonishing to me that there are at least 29 different genes, each involved in a translocation with *MLL* and presumably each leading to a unique fusion gene. Four translocation breakpoints involving *MLL* have been cloned; in each of them, *MLL* is interrupted just 5′ of the zinc finger region, and the 5′ portion of *MLL* is fused to the 3′ portion of the gene from the other chromosome partner, leading to a fusion mRNA and presumably to a fusion or chimeric protein. The critical fusion gene is contained on the derivative 11 (der[11]) chromosome.

In our series of 58 de novo acute leukemia patients with *MLL* rearrangements, we found that 16 had only a single rearranged band, using the 0.74-kb cDNA probe (fig. 2). To distinguish which derivative chromosome was represented by each of the rearranged bands on Southern blot analysis, we amplified sequences by PCR from the centromeric and telomeric portions of the 0.74-kb cDNA fragment to create distinct cDNA probes. The centromeric PCR fragment detected the germ-line band and only one of the rearranged bands, on Southern blot analysis. The rearranged band detected with this probe corresponds to the der(11) chromosome which contains the 5′ portion of the *MLL* gene. The fragment amplified by PCR from the cDNA fragment telomeric to the breakpoint was also hybridized to the same blots. The telomeric probe identified

Table 4

Association of *MLL* Rearrangements and Prior Therapy with Topoisomerase II–reactive Drugs

	No. of Patients with Prior Treatment with Topoisomerase II Inhibitor	
	+	–
MLL rearrangement:		
+	9[a]	0
–	1[b]	2[c]

SOURCE.—Super et al. 1993.

NOTE.—All patients in table 2 had cytogenetically recognized 11q23 rearrangements. The association of *MLL* rearrangements with prior topoisomerase II exposure was statistically significant ($P = .01$ by Fisher's exact test).

[a] All patients had balanced translocations.

[b] Patient had an unbalanced translocation.

[c] Both patients had del(11)(q23).

Table 5

Functional Classification of Transforming Genes at Translocation Junctions

	Location	Translocation	Disease[a]
SRC family (TYR protein kinases):			
ABL	9q34	t(9;22)	CML/ALL
LCK	1p34	t(1;7)	T-ALL
ALK	5q35	t(2;5)	NHL
Serine protein kinase:			
BCR	22q11	t(9;22)	CML/ALL
Cell surface receptor:			
TAN1	9q34	t(7;9)	T-ALL
Growth factor:			
IL2	4q26	t(4;16)	T-NHL
IL3	5q31	t(5;14)	PreB-ALL
Mitochondrial membrane protein:			
BCL2	18q21	t(14;18)	NHL
Cell cycle regulator:			
CCND1 (*BCL1-PRAD1*)	11q13	t(11;14)	CLL/NHL
Myosin family:			
MYH11	16p13	inv(16),t(16;16)	AML-M4Eo
Ribosomal protein:			
EAP (*L22*)	3q26	t(3;21)	t-AML/CML BC
Unknown:			
DEK	6p23	t(6;9)	AML-M2/M4

[a] CML = chronic myeloid leukemia; ALL = acute lymphoblastic leukemia; T-ALL = T-cell ALL; NHL = non-Hodgkin lymphoma; PreB-ALL = pre-B-cell ALL; CLL = chronic lymhocytic leukemia; AML = acute myeloid leukemia; and CML BC = CML in blast crisis.

the germ-line band, as well as the derivative chromosome of the other translocation partner. Clearly in cases with two rearranged bands, both derivative chromosomes are present. However, in the cases in which only one rearranged band is detected, it consistently was identified only by the centromeric probe. The presence of a deletion was confirmed by FISH and by densitometry using a series of probes telomeric to the breakpoint (Kobayashi et al. 1993; Thirman et al. 1993*b*). Therefore, the sequences immediately centromeric to the breakpoint were always preserved, but the sequences distal to the breakpoint appeared to be deleted in 25% of cases.

As I stated earlier, another very intriguing observation related to leukemia with an 11q23 translocation is that this translocation occurs with fair frequency in cancer patients previously treated with topoisomerase II inhibitors (i.e., drugs that inhibit the function of topo II). Analysis of DNA from leukemic cells of these patients shows that the breakpoint occurs in the same region of *MLL* as it does in the leukemias de novo. Heidi Gill Super, a graduate student in the laboratory, has analyzed DNA samples from our lab and from our collaborator in Denmark, Jens Pedersen-Bjergaard, using the 0.74-kb probe (Super et al. 1993). Her results are shown in table 4. You can see the remarkable concordance of the arrangements of *MLL* and prior exposure to topo II. This observation means that we now have the opportunity to study experimentally at least one mechanism leading to chromosome translocations. As I described to you 2 years ago, the genes involved in chromosome translocations belong to a number of categories, summarized in tables 5 and 6. The number of genes has increased dramatically.

There has been a very rapid application of the probes obtained from cloning of the 11q23 translocation breakpoint to using them in a clinical setting. One of the most important applications has been in the analysis of infant leukemia, i.e., leukemia in children under 1 year of age. We knew from cytogenetic studies that 11q23 translocations were very common in infant leukemia. Using the appropriate probes, John Kersey and his associates have now shown that over 70% of all infants, regardless of whether they have acute lymphoblastic leukemia or acute myeloid leukemia, have a rearrangement of *MLL;* for a number of these infants, mate-

Table 6

Structural Classification of Transforming Genes at Translocation Junctions

	Location	Translocation	Disease[a]
		DNA Binding Factors	
Homeobox:			
PBX	1q23	t(1;19)	PreB-ALL
HOX11	10q24	t(10;14)/t(7;10)	T-ALL
Helix-loop-helix:			
CAN	9q34	t(6;9)	AML
LYL1	19p13	t(7;19)	T-ALL
MYC[b]	8q24	t(8;14)	B-ALL/T-ALL
TAL1(SCL)	1p34	t(1;14)	T-ALL
TAL2	9p32	t(7;9)	T-ALL
TCF3(E2A)[b]	19p13	t(1;19)	PreB-ALL
Zinc finger:			
ETO	8q24	t(8;21)	AML-M2
MLL	11q23.3	t(11q23)	ALL/AML
PLZF	11q23.1	t(11;17)	APL
PML	15q22	t(15;17)	APL
RARA	17q12	t(15;17)	APL
EVI1	3q26	inv(3),t(3;3)	AML
BCL6	3q27	t(3;14)	NHL
LIM:			
RBTN1(TTG1)	11p15	t(11;14)	T-ALL
RBTN2	11p13	t(11;14)	T-ALL
Other:			
AML1 (*runt* homology)	21q22	t(8;21),t(3;21)	AML-M2
LYT10 (*rel* homology)	10q24	t(10;14)	B-NHL
Undefined:			
MDS1	3q26	t(3;21)	AML
		Transcriptional Modulators	
BCL3	19q13	t(14;19)	B-CLL
CBFB	16q22	inv(16),t(16;16)	AML-M4Eo

[a] See footnote to table 5.
[b] Also leucine zipper motif.

rial was not available or was inadequate for cytogenetic analysis (Chen et al. 1993). Therefore, the DNA probes were critical for an accurate diagnosis. But of equal importance is the observation that, at least in acute lymphoblastic leukemia, *MLL* gene rearrangements are associated with a very poor prognosis. These infants with an *MLL* rearrangement had a 15% projected event-free survival at a median follow-up of 46 months, compared with 80% in infants with a normal *MLL* gene. Therefore prompt identification of these infants can alert the physician to the need for very aggressive treatment.

Another major mechanism leading to malignant transformation is the loss of function of what we now call "tumor-suppressor genes." This often occurs as a result of chromosome deletion of one allele and an inactivating mutation in the other allele. Many of these tumor-suppressor genes have been mapped because of the association of recurring chromosome deletions with particular tumors (table 7). Others have been detected through the use of DNA markers for determining loss of heterozygosity. Just as there are a large number of genes whose function can be altered through chromosome translocations, there are also a large number of genes that are altered as a result of deletions or mutations. In normal cells, they function in a variety of pathways, including cell cycle regulation and as repressors of genes involved in other aspects of cell growth.

Table 7

Characteristic Rearrangements in Solid Tumors

	Translocations	Genes
Pleomorphic adenoma	t(3;8)(p21C2)	
Liposarcoma (myxoid)	t(12;16)(p13.3;p11.2)	*CHOP*(12p)/*FUS*(16p)
Synovial sarcoma	t(X;18)(p11C1)	*OAT1,2*(Xp)/?
Rhabdomyosarcoma	t(2;13)(q35-37C4)	*PAX3*(2q)/?
Clear cell sarcoma of tendons	t(12;22)(q13C2)	*ATF1*(12q)/*EWS*(22q)
Ewing sarcoma	t(11;22)(q24C2)	*FLI1*(11q)/*EWS*(22q)
Askin tumor	t(11;22)(q24C2)	*FLI1*(11q)/*EWS*(22q)
Peripheral neuroepithelioma	t(11;22)(q24C2)	*FLI1*(11q)/*EWS*(22q)
	Deletions-Inversions	
Meningioma–acoustic neurinoma	del(22)(q12)	*NF2*
Papillary thyroid carcinoma	inv(10)(q11q21)	*RET/PTC-PKA*
Parathyroid adenoma	inv(11)(p15q13)	*PTH/CCND1(PRAD1)*
Retinoblastoma	del(13)(q14q14)	*RB1*
Wilms tumor	del(11)(p13p13)	*WT1*

Clearly the loss of these growth-repressing genes is a critical component of the development of cancer.

There is a very important difference between genes involved in translocations and those that are tumor-suppressor genes, which is of critical importance to geneticists. Except for extremely rare and not-well-documented examples, chromosome translocations are *not* inherited. Mutations or deletions in tumor-suppressor genes, on the other hand, may be inherited in the hemizygous state, and, as far as I know, they are the only class of genes in which inherited defects are associated with a predisposition to particular forms of cancer. It is these families that will be of especial interest but also of concern for clinical geneticists. Cancers related to defects in tumor-suppressor genes were first identified by Alfred Knudson, with whom I shared the Allen Award. What Al proposed in 1971 was that children with retinoblastoma who had an affected parent had inherited one copy of the defective gene, and it just required a mutation in the other allele of that gene to lead to a malignant cell (Knudson 1971). This explained the earlier age of onset of the disease and the multiple tumors in children with a positive family history compared to those with sporadic tumors.

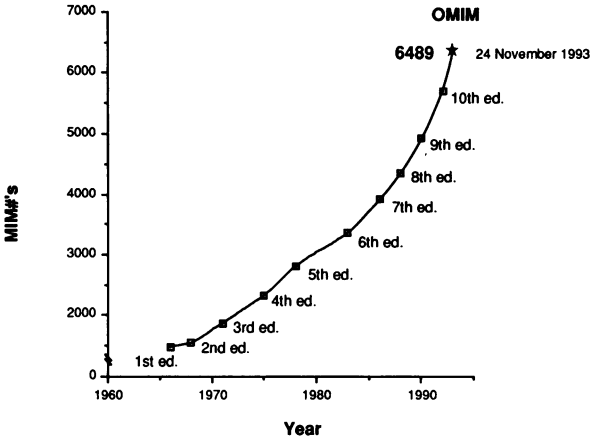

Figure 3 Total number of entries in *Mendelian Inheritance in Man* for each edition, updated to include entries into the *Online Mendelian Inheritance in Man* (OMIM). Reproduced with permission of Dr. Victor McKusick.

As we identify an increasing number of these genes, it will be essential that cancer genetics is integrated not only into oncology, but also into genetics. Just consider the impact on clinical geneticists and genetic counselors of the cloning of the gene that predisposes to breast cancer, ovarian cancer, and possibly to prostate cancer. This is likely to happen in the next 6 to 12 months. Ideally, both oncologists and genetic counselors will be involved in obtaining an accurate family history listing all the individuals who had some genetic defect or tumor, either benign or malignant. Samples of tissue for DNA analysis will be required, and the work-up will be virtually identical to that for patients with Huntington disease, for example. The goal is to detect patients at risk before the symptoms appear. **But** there is a critical difference; you *can* do something to help

presymptomatic cancer patients. You can do that right now. Careful monitoring of individuals at risk can detect the cancers at an early stage, and treatment can be effective; in essence, it can be curative. Of equal importance is the ability to reassure patients who did not inherit the susceptibility gene that they do not need to undergo repeated diagnostic tests which are often painful, as well as expensive, and are a poor use of society's restricted resources for health care. A major consequence of our ability to distinguish carriers from unaffected individuals is the requirement for adequate counseling of individuals in both categories. Here the pilot studies on cystic fibrosis testing will provide us with very important data regarding the deficiencies in our present system of delivery of genetic services. We as a Society, using the term both for us professionally as well as for us as citizens, are woefully unprepared.

Early on in this talk, I described what I perceived as the fragmentation of human genetics in the 1960s. The recent explosion of information regarding cancer genes, as well as many other genes, emphasizes the *unity* of genetics; the conservation of some genes in humans, mouse, *Drosophila,* yeast, and bacteria is well established. Thus, the *MLL* gene at 11q23 that we and others have isolated has been shown to have a high degree of homology to regions of the *Drosophila trithorax* gene, which is the basis for other investigators calling it "*Htrx*" or "*HRX*." Thus, those of us involved in cancer genetics and clinical genetics must be cognizant of the existence of the counterparts of these genes in other organisms. An understanding of their function in these other organisms may provide critical insights into their normal function in human cells and into the consequences of their altered function in malignant cells.

Here we are in 1993. We as geneticists have increasingly sophisticated tools to decipher the nature of the genetic defects in the over 6,000 disorders listed in the 10th edition of Victor McKusick's book, *Mendelian Inheritance in Man* (1992) (fig. 3). Victor has informed me that there are over 6,000 disorders, and he estimates that these represent only about 10% of all genes. It's quite remarkable how the number of identified disorders and mapped genes parallels the increase in the number of human geneticists. I do not look forward to a meeting of over 30,000 geneticists! We have a pool of talented and well-trained geneticists who can translate this information into improved patient care and, where appropriate, into prevention of disease. Can we meet the challenge? Can we all focus on the common goals? Can we understand that the cooperative application of all of our skills can lead to a major improvement in our patients' lives? We are living in the golden age of the biomedical sciences. We must use our resources wisely, and we must, and I am confident that we will, meet the challenge.

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